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Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 18 (2007) 2399–2408

Enantioselective resolution of chiral aromatic acids by biphasic recognition chiral extraction

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Received 17 July 2007; revised 10 September 2007; accepted 20 September 2007

Abstract—This paper reports a new chiral separation technology—biphasic recognition chiral extraction for the separation of aromatic acid enantiomers such as α-cyclohexyl-mandelic acid (CHMA) and naproxen (NAP). The biphasic recognition chiral extraction system was established by adding hydrophobic D(L)-isobutyl tartrate in 1,2-dichloroethane organic phase and hydrophilic β-cyclodextrin (β-CD) derivative in aqueous phase, which preferentially recognize the (*R*)-enantiomer and (*S*)-enantiomer, respectively. These studies involve an enantioselective extraction in a biphasic system, where aromatic acid enantiomers form complexes with the β-cyclodextrin derivative in the aqueous phase and D(L)-isobutyl tartrate in the organic phase, respectively. Factors affecting the extraction mechanism are analyzed, namely the influence of the concentrations of the extractants and aromatic acid enantiomers, the types of the extractants, pH, and temperature. The experimental results show that the biphasic recognition chiral extraction is of much stronger chiral separation ability than the monophasic recognition chiral extraction, which utilizes the cooperations of the forces of the tartrate and the β-CD derivative. Hydroxypropyl-β-cyclodextrin (HP-β-CD), hydroxyethyl-β-cyclodextrin (HE-β-CD), and methyl-β-cyclodextrin (ME-β-CD) have stronger recognition abilities for the (*S*)-aromatic acid enantiomers than those for (*R*)-aromatic acid enantiomers, among which HP-β-CD has the strongest ability. D-Isobutyl tartrate preferentially recognizes (*R*)-CHMA and (*S*)-NAP, while L-isobutyl tartrate preferentially recognizes (*S*)-CHMA and (*R*)-NAP. The maximum enantioselectivities of CHMA and NAP are 2.49 and 1.65, under conditions at which the pH values of the aqueous phases are 2.7 and 2.5, at the ratio of 2:1 of [isobutyl tartrate] to [HP-β-CD].

1. Introduction

Life on earth is based on biomolecules, such as enzymes, proteins, and DNA that are all of a single handedness. As a consequence, the left- and right-handed enantiomers of chiral, bioactive compounds exhibit different physiological effects on pharmacological activity, metabolism process, and toxicity when ingested by living organisms.[1] For example, while one enantiomer of a pharmaceutical can be therapeutic, the other can be toxic. Recently there are more than 50% of clinical drugs with chiral elements, more than 85% of which exist as racemic mixtures. Therefore, there is an increasing demand for enantiomerically pure enantiomers in the chemical industry.[2]

Preparative separation is an important method for obtaining single enantiomer drugs.[3,4] Many researchers have attempted the separation of optically active compounds.[5] Such chiral separation technologies such as crystallization, chromatography, kinetic resolution, etc. accelerate research regarding chiral compounds, but there still exist some problems for most racemic compounds. Membrane-based approaches will most certainly become very important for continuous operation, but at the moment still suffer from being generally less enantioselective.[6] Elemér Fogassy reported non-conventional methods for the resolution of enantiomers.[7]

Chiral solvent extraction follows certain rules for the choice of separation system and has a large application range. As a potential large scale production technique, chiral solvent extraction has attracted the attention of many researchers to make great efforts in recent years.[8–14] The separation factor (α) is the most important parameter for chiral extraction, which directly influences the separation effect. For example, for a 99% pure product ($R/S = 100$) about 190 NTU (number of transfer units) are required for an enantioselectivity of 1.05, a number decreasing to

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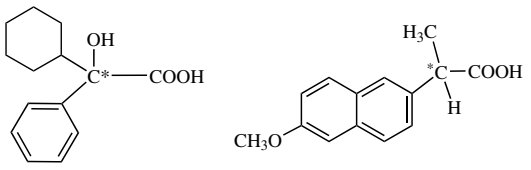
doi:10.1016/j.tetasy.2007.09.031

approximately 30 when α increases to a value of 1.20.[15] In fact α depends on the difference in free energy $-\Delta(\Delta G)$, so how to increase $-\Delta(\Delta G)$ has become an urgent problem to be resolved. As is well known, the chiral extractants play the most important role in the separation efficiency. There are several normal chiral extractants, such as tartaric acid derivatives,[16] crown ethers,[17] cholesteryl L-glutamate,[18] cyclodextrins,[19] and so on.[13] However, the enantioselectivities of the chiral extractants are somewhat low, and a large number of transfer units are required in chiral solvent extraction processes. Until now, few new types of extractants have been tested to separate enantiomers. The search for new extraction techniques with high enantioselectivity should speed up the application of chiral solvent extraction, and realize large scale production with low energy cost.

α-Cyclohexyl-mandelic acid (CHMA) is a significant chiral drug precursor, which is used to synthesize chiral drugs, such as oxybutynin, which is the principal drug for curing urinary incontinence and has a wide market. Due to the (*S*)-enantiomer having a better drug effect and lower side effects than the racemic mixture, it is necessary to either resolve racemic mixture or esterify the chiral precursor (*S*)-CHMA in order to obtain (*S*)-oxybutynin; the latter can reduce the cost greatly. Naproxen (NAP), 6-methoxy-α-methyl-2-naphthaleneacetic acid is a non-steroidal anti-inflammatory drug with analgesic and *anti*-pyretic properties.[20] It has one stereogenic center which gives rise to two optical isomers in which pharmacological activity resides in the (*S*)-enantiomer, while the (*R*)-enantiomer causes some unwanted side effects.[21]



Structure of α-cyclohexyl-mandelic acid and Naproxen

Herein, we report a new chiral separation technology—biphasic recognition chiral extraction for the separation of aromatic acid enantiomers, such as CHMA and NAP. As the two chiral extractants of hydrophobic tartrate and hydrophilic β-CD derivative with oppositely preferential recognition direction are added to the organic phase and aqueous phase, biphasic recognition chiral extraction is of a much stronger chiral separation force than monophasic recognition chiral extraction, which utilizes the cooperations of the forces of tartrate and β-CD derivative. This work has been carried out for preparation for the preparative separation of aromatic acid enantiomers.

2. Results and discussion

2.1. Study on chiral recognition direction of extractants

The distribution coefficient (k) and separation factor (α) for aromatic acid enantiomers (CHMA and NAP) were investigated in several chiral extraction systems containing a β-CD derivative (HP-β-CD, HE-β-CD or ME-β-CD) in the aqueous phase and isobutyl tartrate in the organic phase (in Table 1). A number of significant observations may be gleaned from Table 1. First, in the chiral extraction systems containing the β-CD derivative (HP-β-CD, HE-β-CD or ME-β-CD) in the aqueous phase and without tartrate (L-tartrate or D-tartrate) in the organic phase, k_R values are always larger than k_S, namely $\alpha > 1$, which indicates that three β-CD derivatives have a stronger recognition ability for (*S*)-enantiomers than for (*R*)-enantiomers. Second, HP-β-CD is of the strongest recognition ability among HP-β-CD, HE-β-CD, and ME-β-CD.

It was also observed (Table 1) that the α-value for CHMA enantiomers could be improved by adding D-isobutyl tartrate in organic phase, but it decreased by adding L-isobutyl tartrate, which indicates that D-isobutyl tartrate preferentially recognize (*R*)-CHMA. But α for NAP enantiomers was improved by adding L-isobutyl tartrate in organic phase, it decreased by adding D-isobutyl

Table 1. k and α of CHMA and NAP enantiomers in different extraction systems

Hydrophobic extractant	Hydrophilic extractant	CHMA[a]			NAP[b]		
		k_S	k_R	α	k_S	k_R	α
D-IBTA	HP-β-CD	0.98	2.44	2.49	5.74	7.06	1.23
	HE-β-CD	0.93	1.52	1.63	7.26	8.55	1.17
	Me-β-CD	0.50	0.98	1.96	6.72	7.13	1.06
	None	13.3	18.4	1.38	29.4	28.6	0.97
L-IBTA	HP-β-CD	1.35	2.37	1.76	5.40	8.91	1.65
	HE-β-CD	0.79	1.14	1.44	6.78	9.98	1.32
	Me-β-CD	0.34	0.45	1.35	12.4	14.4	1.16
	None	13.4	12.6	0.94	39.2	47.2	1.15
None	HP-β-CD	0.31	0.61	1.95	2.86	3.72	1.30
	HE-β-CD	0.35	0.53	1.51	3.10	3.78	1.22
	Me-β-CD	0.19	0.31	1.63	5.47	6.05	1.10
	None	—	—	—	—	—	—

Aqueous phase: [β-cyclodextrin(CD) derivative] = 0.1 mol L^{-1}, temperature: 5 °C.
[a] pH 2.7.
[b] pH 2.5, [CHMA] = [NAP] = 1 mmol L^{-1}; organic phase: [isobutyl tartrate] = 0.2 mol L^{-1}.

tartrate, which indicates that L-isobutyl tartrate preferentially recognizes (*R*)-NAP. As a result, in the biphasic recognition chiral extraction system for the separation of CHMA enantiomers, hydroxypropyl-β-cyclodextrin and D-isobutyl tartrate were chosen as chiral selectors in the aqueous phase and the organic phase, while for separation of NAP enantiomers, hydroxypropyl-β-cyclodextrin and L-isobutyl tartrate are chosen as chiral selectors.

Finally, in biphasic recognition chiral extraction, the enantioselectivities for CHMA and NAP enantiomers are 2.49 and 1.65, but in the monophasic recognition chiral extraction system containing tartrate in the organic phase, α for CHMA and NAP are only 1.38 and 1.15, respectively. Figure 1 shows the chromatograms of CHMA enantiomers before and after extraction. It was found that ee of (*S*)-CHMA in the aqueous phase reached 27.6% by one stage extraction, k_R, k_S, and α are 2.44, 0.89, and 2.49, respectively. In general, α is under 1.2 in the monophasic recognition chiral extraction system containing D-/L-tartrate.[8,9,16] It can be concluded that the biphasic recognition chiral extraction is of much stronger chiral separation ability than the monophasic recognition chiral extraction, which is in agreement with the theory.

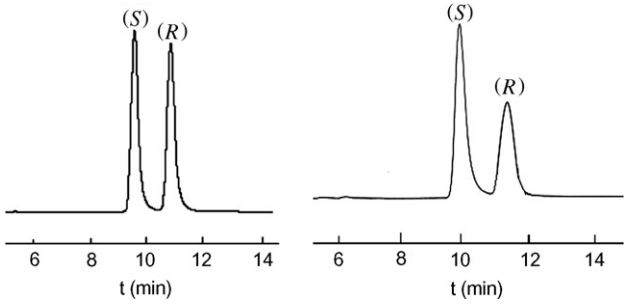


Figure 1. Chromatograms of CHMA enantiomers before and after extraction. Organic phase: [D-isobutyl tartrate] = 0.2 mol L^{-1}, aqueous phase: [HP-β-CD] = 0.1 mol L^{-1}, pH 2.7, and temperature 5 °C.

2.2. Influence of tartrate concentration

The influence of the concentration of tartrate in the organic phase on extraction efficiency is summarized in Figures 2 and 3. When tartrate was not added to the organic phase, HP-β-CD showed the enantioselectivities on CHMA and NAP enantiomers, but with small distribution coefficients. With an increase of tartrate content, the distribution coefficients for all of the aromatic acid enantiomers were greatly increased. Meanwhile, all the enantioselectivities increased before the concentration of tartrate was up to 0.2 mol L^{-1}. When increasing the concentration of tartrate is increased further, the distribution coefficients increased continuously, while the enantioselectivities followed an opposite tendency. This is because a larger amount of complexes for CHMA and NAP enantiomers were formed in the organic phase which led to an increase of the distribution coefficients, and the enantioselectivities are the results of the cooperation of HP-β-CD in the aqueous phase and tartrate (L-tartrate or D-tartrate) in organic phase. It can be concluded that the maximum enantioselectivities of CHMA and NAP enantiomers are achieved in 2:1 ratio of the molar concentrations of tartrate to HP-β-CD.

2.3. Influence of HP-β-CD concentration

HP-β-CD has chiral recognition ability for (*R*)-enantiomer and (*S*)- enantiomer due to its special structure, so it plays an important role in biphasic recognition chiral extraction. HP-β-CD can form complexes with (*R*)- and (*S*)-enantiomers, which not only improves the solubility of the enantiomers in buffer solution, but also has a great effect on distribution behavior of enantiomers in biphasic recognition chiral extraction system. As a result HP-β-CD concentration has a great influence on *k* and α.

Figures 4 and 5 show the influence of the concentration of HP-β-CD in the aqueous phase on extraction efficiency. A number of significant results have been achieved from

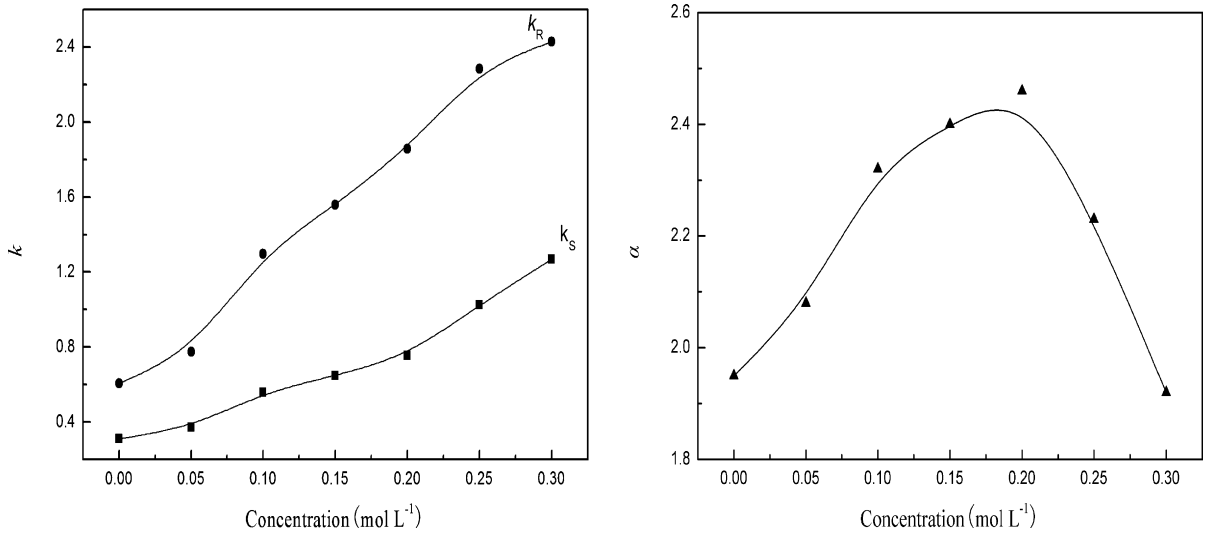


Figure 2. Effect of the concentration of D-tartrate on *k* and α for CHMA enantiomers. Aqueous phase: [HP-β-CD] = 0.1 mol L^{-1}, pH 2.7 and temperature 5 °C.

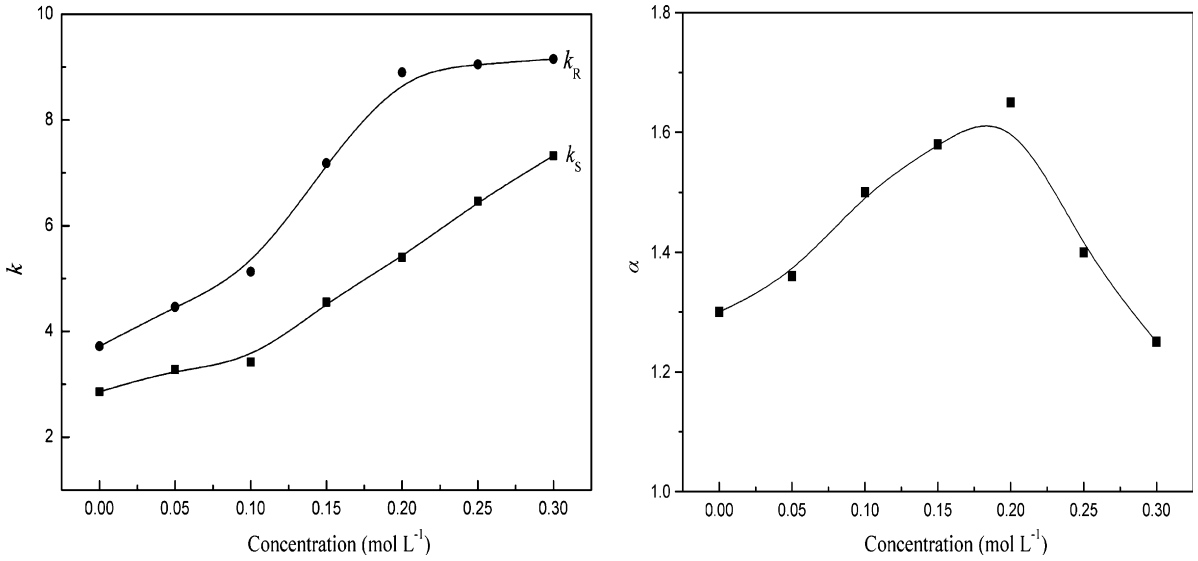


Figure 3. Effect of the concentration of L-tartrate on k and α for NAP enantiomers. Aqueous: phase [HP-β-CD] = 0.1 mol L^{-1}, pH 2.5, and temperature 5 °C.

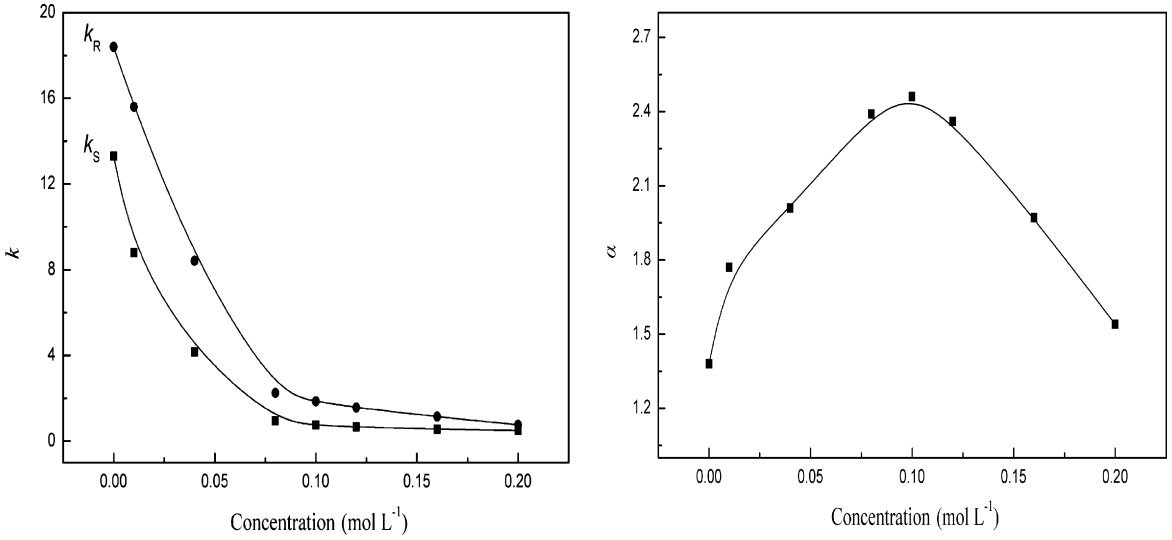


Figure 4. Influence of HP-β-CD concentration on k and α for CHMA enantiomers. Organic phase: [D-isobutyltartrate] = 0.2 mol L^{-1}, pH 2.7, and temperature: 5 °C.

Figures 4 and 5. First, with the increase of the concentration of HP-β-CD, the distribution coefficients for all of the aromatic acid enantiomers decrease greatly, which can be explained by the higher amount of complexes formed in the aqueous phase. Second, all the enantioselectivities increased remarkably before the concentration of HP-β-CD was up to 0.1 mol L^{-1}. It was also observed that the distribution coefficients and enantioselectivities continuously decrease with a further increase in the concentration of HP-β-CD. Finally, the enantioselectivities of CHMA and NAP enantiomers reach a maximum at the ratio of 2:1 of the molar concentrations of tartrate to HP-β-CD. The enantioselectivities can be explained by the results of the cooperation of HP-β-CD in the aqueous phase and tartrate (L-tartrate or D-tartrate) in the organic phase, which is in accordance with the above results.

2.4. Influence of pH

All aromatic acid enantiomers [(*R*)- or (*S*)-CHMA and NAP] have one carboxylic group and an aromatic group. One dissociation equilibrium exists in aqueous solutions:

$$\mathrm{ArR_1CR_2COOH} \overset{K_a}{\leftrightarrow} \mathrm{ArR_1CR_2COO^-} + \mathrm{H^+} \qquad (1)$$

The dissociation constant for Eq. 16 can be described by

$$K_a = \frac{[\mathrm{A^-}][\mathrm{H^+}]}{[\mathrm{A}]} \qquad (2)$$

where A and $\mathrm{A^-}$ are the unionized and anion of (*R*)- and (*S*)-aromatic acid, respectively.

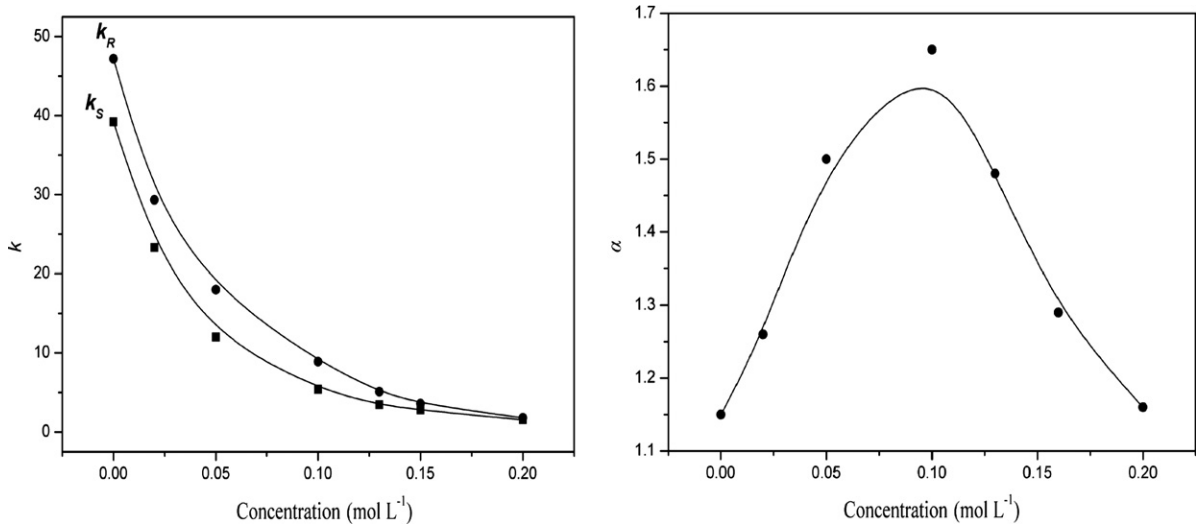


Figure 5. Influence of HP-β-CD concentration on k and α for NAP enantiomers. Organic phase: [L-isobutyl tartrate] = 0.2 mol L^{-1}, pH 2.5, and temperature: 5 °C.

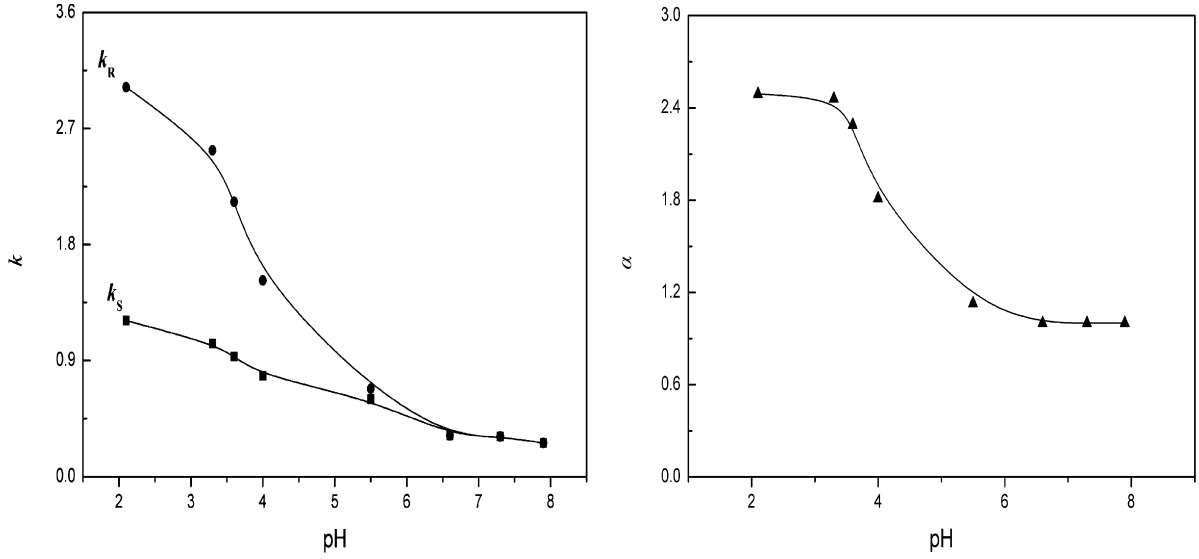


Figure 6. Influence of pH on k and α for CHMA enantiomers. Organic phase: [D-isobutyl tartrate] = 0.2 mol L^{-1}; aqueous phase: [HP-β-CD] = 0.1 mol L^{-1}, and temperature: 5 °C.

To understand better the effect of pH on the distribution behavior of CHMA and NAP enantiomers in the presence of the selective mechanism of extraction, k_R, k_S, and α for CHMA and NAP enantiomers were studied in the biphasic recognition chiral extraction system. The results are shown in Figures 6 and 7. This new organization of the results, as a function of pH, allows us to observe more clearly that all the distribution coefficients of CHMA and NAP enantiomers decrease when increasing the pH of the aqueous phase. Regarding the enantioselectivities of the extraction process, it was also observed that all α-values decrease when increasing the pH value.

The possible reasons for these may be that the amount of ionic CHMA or NAP increases with the rise of the pH. HP-β-CD and isobutyl tartrate mainly have chiral recognition ability and affinity for molecular CHMA and NAP, but not for ionic CHMA and NAP. Ionic CHMA and NAP only exist in the aqueous phase. The concentration of complexes formed by isobutyl tartrate and enantiomers decreases with an increase in the pH. As a result k_R, k_S, and α greatly decrease with the rise of the pH. Therefore, it should be kept at low pH to carry out the extraction process.

2.5. Influence of aromatic acid enantiomers concentration

The influence of the aromatic acid enantiomers concentration on extraction efficiency was partly investigated with racemic naproxen as the solute. Figure 8 shows the influence of naproxen concentration on the distribution behavior of NAP. All distribution coefficients were enhanced

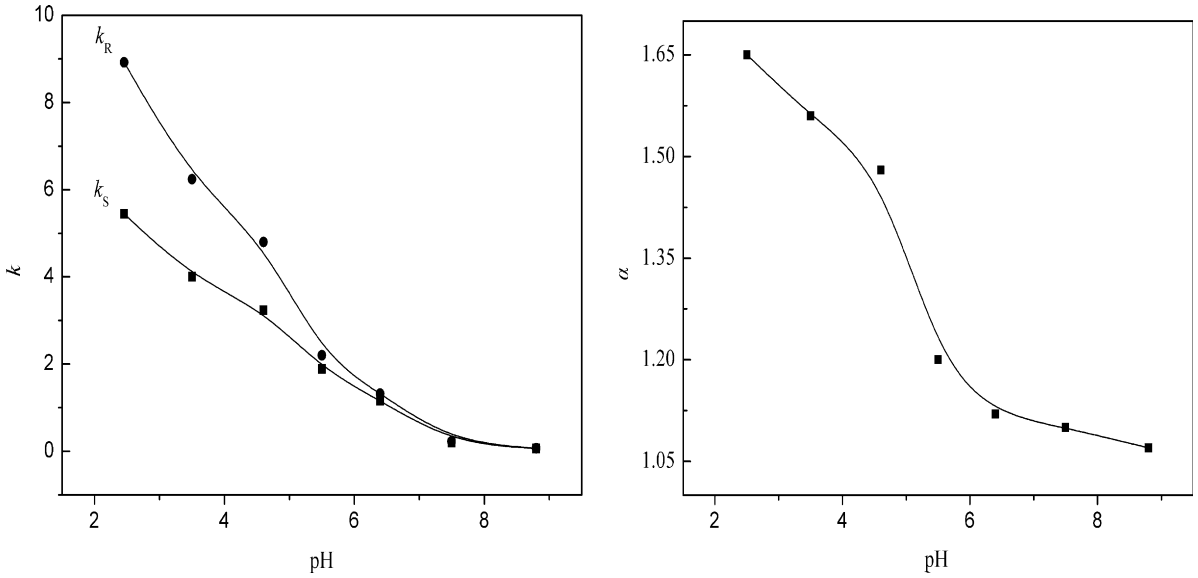


Figure 7. Influence of pH on k and α for NAP enantiomers. Organic phase: [L-isobutyl tartrate] = 0.2 mol L^{-1}; aqueous phase: [HP-β-CD] = 0.1 mol L^{-1}, and temperature: 5 °C.

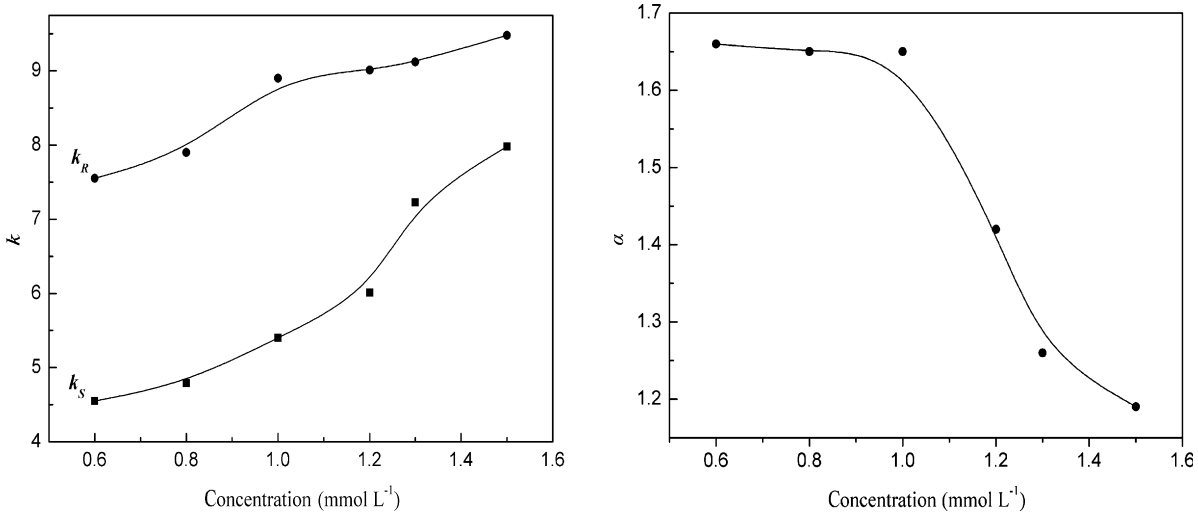


Figure 8. Effect of initial concentration of NAP on k and α. Organic phase: [L-isobutyl tartrate] = 0.2 mol L^{-1}; aqueous phase: [HP-β-CD] = 0.1 mol L^{-1}, pH 2.5, and temperature: 5 °C.

upon an increase of the initial concentration of the solutes. However, the values of enantioselectivities are relatively higher at low concentrations, which indicates a better enantioseparation efficiency at low initial concentrations.

2.6. Influence of temperature

The influence of temperature on the distribution behavior was partly investigated in the range of 5–30 °C with racemic naproxen as the solute. Table 2 shows that higher temperatures led to an increase in the distribution coefficients and a decrease in enantioselectivities.

Figure 9 shows the variations of $\ln k$ and $\ln \alpha$ versus $1/T$. The results can be described as fitting very well with the Van't Hoff model, indicating that the complexes do not change in conformation and that enantioselective interactions remain unchanged in the temperature range studied.[22]

Table 2. Influence of the temperature on the enantioseparation of NAP enantiomers

Temp. (°C)	k_R	k_S	α
5	5.4	8.9	1.65
10	7.5	10.4	1.39
15	9.8	12.5	1.28
20	11.5	13.4	1.16
25	13.8	15.2	1.10
30	17.7	18.9	1.05

Organic phase: [L-isobutyl tartrate] = 0.2 mol L^{-1}, aqueous phase: [HP-β-CD] = 0.1 mol L^{-1}, pH 2.5.

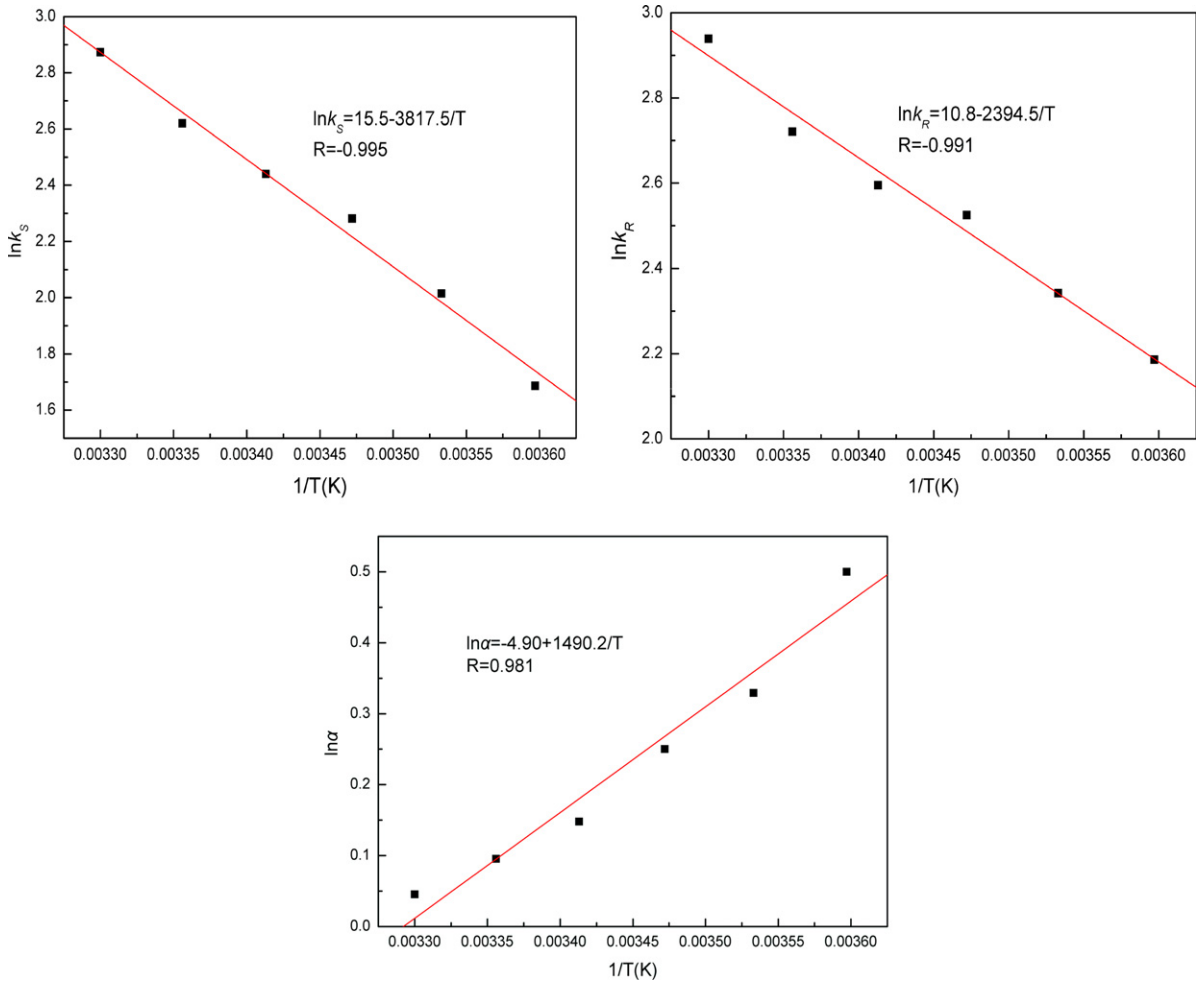


Figure 9. Influence of temperature on the enantioseparation of naproxen. Organic phase: [L-isobutyl tartrate] = 0.2 mol L^{-1}; aqueous phase: [HP-β-CD] = 0.1 mol L^{-1}, pH 2.5.

3. Conclusion

A new chiral separation technique—biphasic recognition chiral extraction has been developed and used for separation of aromatic acid enantiomers such as CHMA and NAP. As hydrophobic tartrate and hydrophilic β-CD derivative with oppositely preferential recognition direction are added to the organic phase and aqueous phase, respectively, the separation ability of the biphasic recognition chiral extraction attributes to the cooperations of the separation abilities of tartrate and β-CD derivative. As a result, the biphasic recognition chiral extraction has a much stronger chiral separation ability than monophasic recognition chiral extraction. The enantioselectivities for CHMA and NAP enantiomers can be greatly improved upon by biphasic recognition chiral extraction.

It was found that the three β-CD derivatives of HP-β-CD, HE-β-CD, and ME-β-CD have stronger recognition abilities for (*S*)-aromatic acid enantiomers than those for (*R*)-aromatic acid enantiomers, among which HP-β-CD has the strongest ability. D-Isobutyl tartrates preferentially recognize (*S*)-CHMA, while L-isobutyl tartrates preferentially recognize (*R*)-NAP. Several factors including the concentrations of the extractants and aromatic acid enantiomers, pH, and temperature influence the extraction efficiency. The maximum enantioselectivities of 2.49 and 1.65 for CHMA and NAP could be achieved, with pH values of the aqueous phases being 2.7 and 2.5, at the ratio of 2:1 of [isobutyl tartrate] to [HP-β-CD]. It can be envisioned that the biphasic recognition chiral extraction will allow enantioselective separations of various organic compounds.

4. Experimental and theoretical

4.1. Materials

Hydrophilic extractants, hydroxypropyl-β-cyclodextrin (HP-β-CD), hydroxyethyl-β-cyclodextrin (HE-β-CD), and methyl-β-cyclodextrin (ME-β-CD) were bought from Xinda Fine Chemical & Co. Inc. (Shandong, China). D- and L-tartrate acids with a purity >99.85% were purchased from Shanghai Xinpu Chemical Factory (Shanghai, China). The hydrophobic extractants, D- and L-isobutyl tartrate, were prepared as described in the literature,[23] from D- and L-tar-

trate acid. α-Cyclohexyl-mandelic acid (CHAM) was purchased from Guangde Keyuan Chemical Co., Ltd (Guangde, China), with purity >98% and melting point 163–164 °C. Naproxen enantiomers (NAP) were brought from Xianju Chemical & Co. Inc. (Zhejiang, China). All other chemicals are of analytical-reagent grade.

4.2. Extraction experiments

HP-β-CD, HE-β-CD, and ME-β-CD were used as the extractants in the aqueous phase. The aqueous phases were prepared by dissolving β-cyclodextrin derivatives (HP-β-CD, HE-β-CD, and ME-β-CD) and aromatic acid enantiomers (CHMA and NAP) in a 0.1 mol L^{-1} phosphate salt buffer solution. D- and L-isobutyl tartrates were used as the extractants in organic phases and dissolved in 1,2-dichloroethane to prepare the organic phases. The equilibrium experiments were performed in 10 mL glass-stoppered tube. Equal volumes (each 3.0 mL) of the organic and aqueous phases were placed in a glass-stoppered tube together, and shaken sufficiently (2 h) before being kept in a water bath (24 h) at a fixed temperature to reach equilibrium. After phase separation, the concentrations of aromatic acid enantiomers (CHMA or NAP) in the aqueous phase were analyzed by HPLC. The total amount of each enantiomer in the organic and aqueous phases after extracting was consistent with their initial amount included in the aqueous phase. Each experiment was duplicated under identical conditions and the standard deviation is in the range of 2%. Since the change in volume is very small, it can be seen as negligible. The concentration of aromatic acid enantiomers (CHMA or NAP) in organic phase is calculated by subtractive method.

4.3. Analytical method

The quantification of aromatic acid enantiomers (CHMA and NAP) in the aqueous phase was performed by HPLC using a UV detector (Merck, Hitachi, Japan) at the UV wavelengths of 254 nm for NAP and 220 nm for CHMA. The column was Lichrospher C18, 5 μm particle size of the Packing Material, 250 mm × 4.6 mm I.D. (Hanbon Science & Technology Co. Ltd). The mobile phase for NAP enantiomers was 0.5% acetic acid buffer solution (pH 3.5)/ethanol (85:15) containing 25 mmol L^{-1} HP-β-CD at a flow of 1.0 mL min^{-1}. The pH of the aqueous phases was measured with a pH electrode and a pH meter (Orion, model 720A, USA). The mobile phase for CHMA enantiomers was 0.075 mol L^{-1} KH_2PO_4 aqueous solution: alcohol: methy1 cyanide (65:20:15) containing 9.5 mmol L^{-1} β-CD at a flow of 1.0 mL min^{-1}. The retention times of the (*S*)-enantiomers are less than that of the (*R*)-enantiomers.

4.4. Theoretical

Distribution coefficient (k), separation factor (α) and the difference in free energy between the two diastereomeric complexes ($-\Delta(\Delta G)$) are important parameters to estimate the chiral solvent extraction performance of extractant, which can be calculated by the following formulas:

$$k_S = C_{O,S}/C_{W,S} \quad (3)$$

$$k_R = C_{O,R}/C_{W,R} \quad (4)$$

$$\alpha = k_R/k_S \quad \text{or} \quad \alpha = k_S/k_R \quad (5)$$

$$-\Delta(\Delta G) = RT\ln\alpha \quad (6)$$

among which $C_{O,S}$ and $C_{W,S}$ represent the concentrations of the (*S*)-enantiomer in the organic phase and aqueous phase, respectively; $C_{O,R}$ and $C_{W,R}$ represent the concentrations of the (*R*)-enantiomer in the organic phase and aqueous phase, respectively; k_R and k_S represent the distribution coefficients of the (*R*)-enantiomer and (*S*)-enantiomer, respectively.

In the monophasic recognition chiral extraction system (chiral selector only in the organic phase), chiral solvent extraction is carried out by the formation of two diastereomeric complexes between chiral selectors and (*RS*)-enantiomers due to such molecular interactions as hydrogen bond polarization, induction, or electrostatics (Fig. 10). The carboxylic acid group of an aromatic acid can donate protons for hydrogen bonding, while tartrate can behave as a proton acceptor due to the oxygen atoms. Since there exist hydrogen bonds between (*RS*)-enantiomers and chiral selectors,

$$R + D \rightleftharpoons R\text{-}D \quad (7)$$

$$S + D \rightleftharpoons S\text{-}D \quad (8)$$

or

$$R + L \rightleftharpoons R\text{-}L \quad (9)$$

$$S + L \rightleftharpoons S\text{-}L \quad (10)$$

In the monophasic recognition chiral extraction system, separation of the (*R*)-enantiomer and (*S*)-enantiomer can be attributed mainly to the difference in $-\Delta(\Delta G)$ between the two diastereomeric complexes in organic phase

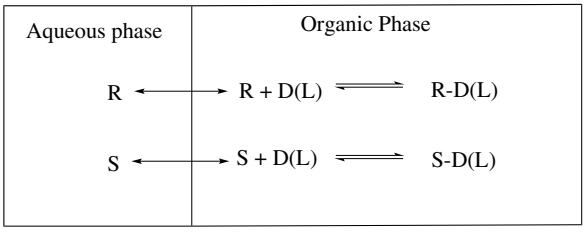


Figure 10. Diagram of the resolution of enantiomers by monophasic recognition chiral extraction.

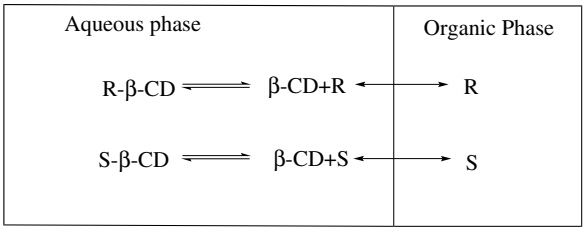


Figure 11. Diagram of the resolution of enantiomers by monophasic recognition chiral extraction.

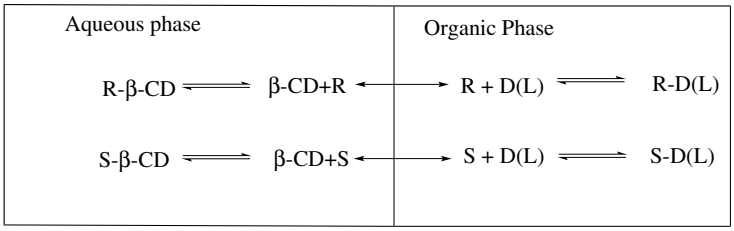


Figure 12. Diagram of the resolution of enantiomers by biphasic recognition chiral extraction.

$$-\Delta(\Delta G)_{\mathrm{D}} = -\Delta G_{R\text{-D}} - (-\Delta G_{S\text{-D}}) = RT\ln\alpha_{\mathrm{D}} \quad (11)$$

$$-\Delta(\Delta G)_{\mathrm{L}} = -\Delta G_{R\text{-L}} - (-\Delta G_{S\text{-L}}) = RT\ln\alpha_{\mathrm{L}} \quad (12)$$

It was found that D-tartrate has a higher recognition ability for (*R*)-CHMA than for (*S*)-CHMA, while L-tartrate has higher recognition ability for (*R*)-NAP than for (*S*)-NAP. As a result $-\Delta(\Delta G)_{\mathrm{D}} > 0$ for CHMA, and $-\Delta(\Delta G)_{\mathrm{L}} > 0$ for NAP.

Feitsma found that CHMA and NAP enantiomers were all well separated on the β-CD stationary phase.[21,24] Furthermore, the experimental results show β-CD derivatives have inclusion with CHMA and NAP enantiomers. Therefore, in the monophasic recognition chiral extraction system without a chiral extractant in the organic phase and with β-CD derivatives in aqueous phase, β-CD derivatives in the aqueous phase have a recognition ability for CHMA and NAP enantiomers and form two diastereomeric complexes with them, respectively (Fig. 11).

$$R + \beta\text{-CD} \rightleftharpoons R\text{-}\beta\text{-CD} \quad (13)$$

$$S + \beta\text{-CD} \rightleftharpoons S\text{-}\beta\text{-CD} \quad (14)$$

β-CD derivatives have a higher recognition ability for the (*S*)-enantiomers than for the (*R*)-enantiomers. This means that β-CD derivatives preferentially recognize (*S*)-enantiomers. The difference in $-\Delta(\Delta G)$ between the two diastereomeric complexes in aqueous phase is given by

$$-\Delta(\Delta G)_{\beta\text{-CD}} = -\Delta G_{S\text{-}\beta\text{-CD}} - (-\Delta G_{R\text{-D}}) = RT\ln\alpha_{\beta\text{-CD}} \quad (15)$$

Then, $-\Delta(\Delta G)_{\beta\text{-CD}} > 0$.

In the biphasic recognition chiral extraction system, the extraction performance is not only related to recognition of the chiral selector in the organic phase for the (*R*)-enantiomers and the (*S*)-enantiomers, but also that of β-CD derivatives in aqueous phase. It is clear that only when the chiral selectors in organic phase and aqueous phase preferentially recognize the (*R*)-enantiomers and (*S*)-enantiomers, respectively, the separation ability is improved greatly in the biphasic recognition chiral extraction. In the biphasic recognition chiral extraction system for the separation of CHMA and NAP enantiomers, β-CD derivatives are added to the aqueous phase as the chiral selector, while D-tartrate and L-tartrate are chiral selectors in the organic phase for CHMA and NAP, respectively (Fig. 12).

Thus, the driving forces for separation of CHMA and NAP enantiomers in the biphasic recognition chiral extraction system are given by

$$-\Delta(\Delta G) = -\Delta(\Delta G)_{\mathrm{D}} + (-\Delta(\Delta G)_{\beta\text{-CD}}) = RT\ln\alpha \quad (16)$$

$$-\Delta(\Delta G) = -\Delta(\Delta G)_{\mathrm{L}} + (-\Delta(\Delta G)_{\beta\text{-CD}}) = RT\ln\alpha \quad (17)$$

As $-\Delta(\Delta G)_{\mathrm{D}}$, $-\Delta(\Delta G)_{\mathrm{L}}$, and $-\Delta(\Delta G)_{\beta\text{-CD}}$ are all over 0, the driving forces $-\Delta(\Delta G)$ for the separation of CHMA and NAP enantiomers are all larger in the biphasic recognition chiral extraction system than those in the monophasic recognition chiral extraction system. As a result, α-values for the biphasic recognition chiral extraction are improved greatly. Therefore, in theory, it can be assumed that the biphasic recognition chiral extraction has a stronger separation ability than the monophasic recognition chiral extraction.

Acknowledgment

This work was supported by the National Natural Science Foundation of China (20776038).

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